PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 31 MAR 2006
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Applicant's or agent's file reference ABL-017-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)
International application No. PCT/BE 03/00189	International filing date *(day/month/year)* 07.11.2003	Priority date *(day/month/year)* 07.11.2003

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61K39/395 C12N15/13 C07K19/00 A61P35/00 C07K16/18 G01N33/577

Applicant
ABLYNX N.V. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.05.2005	30.03.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Le Flao, K Telephone No. +31 70 340-1040

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-57 as originally filed

Claims, Numbers

1-45 as originally filed

Drawings, Figures

1-9 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 14-16 (totally) and 18,19,33 (partially)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 14-16 (totally) and 18,19, 33 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13,17-45
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13,17-45
Industrial applicability (IA)	Yes:	Claims	1-13,17-45
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reference is made to the following documents:

D1: US 2002/058033 A1 (Bonner J et al) 16 May 2002

D2: ARBABI GHAHROUDI M ET AL: "Selection and identification of single domain antibody fragments from camel heavy-chain antibodies" FEBS LETTERS, vol. 414, no. 3, 15 September 1997, pages 521-526, XP002066903

D3: US 2003/092892 A1 (Howell S et al) 15 May 2003

D4: CORTEZ-RETAMOZO V ET AL: "Efficient tumor targeting by single-domain antibody fragments of camels" INTERNATIONAL JOURNAL OF CANCER, vol. 98, no. 3, 20 March 2002, pages 456-462, XP002248403

Claims 1-13 and 17-45 are novel since they relate to single domain antibody against EGFR and uses thereof, which are not disclosed in any of the cited documents.

1. Lack of inventive step: claims 1-9, 17-45

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 does not involve an inventive step in the sense of Article 33(3) PCT.

The document **D1** is regarded as being the closest prior art to the subject-matter of claim 1, and discloses (the references in parentheses applying to this document) anti EGFR human single chain antibodies (scFv, §45) isolated by screening phage library. Such antibodies are used to detect breast cancer tumours (§93).

The subject-matter of claim 1 therefore differs from these known antibodies in that it comprises at least one single domain antibody, with specific sequences. The effect of the difference is that it is an alternative form of antibody.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative form of anti EGFR antibodies. The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

Document **D2** discloses the immunisation of dromedary with tetanus toxoid and lysozyme, the isolation of mRNA from the blood, the construction of a library and the selection of soluble VHH fragments. The interest of such VHHs for preparing multivalent binders having an increased avidity is mentioned (p.521, right-hand column, §4,5 ; p.522, left-hand column ; p.525, right-hand column, §3). It is therefore considered that the skilled person when trying to solve the problem posed would apply the teaching of D2 for obtaining a VHH antibody anti EGFR. The preparation of VHHs antibodies itself is not considered inventive since it is known from many documents published before the filing date describing such a method (see also WO03/054016). Applying a known technique for preparing antibodies to another particular protein, here EGFR, is not considered to require inventive skills.

However part of claim 2 is considered as involving an inventive step for the following reason. The fact that in example 7 it has been shown that recombinant nanobody EGFRIIIa42 is able to internalize Her-14 but not 3T3 cells is a particular property supporting the inventive step of part of claim 2. Should the applicant submit data showing unexpected properties to the 22 anti EGFR disclosed in the application, an inventive step may be recognized for claim 2. Otherwise restriction to the particular example is required.

Dependent claims 3 and 4 dealing with polypeptide further comprising a single domain antibody directed against a serum protein or against IFN-gamma, TNF-alpha, IFN-gamma receptor or TNF-alpha receptor do not appear to involve an inventive step since document D2 discloses the interest of having multivalent VHHs.

Dependent claims 5-9 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step. The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claim 17, which therefore is also considered not inventive.

Claims 18-36 relating to the therapeutical use and the diagnostic use of the antibodies is anticipated by D1 which discloses the detection of breast cancer with anti EGFR antibodies and describes the therapeutical uses for treating cancers. Such claims are therefore not considered to involve an inventive step. Neither are claims 37-45 related to the use, the method for producing a polypeptide, a kit and a therapeutic composition.

2. Inventive step and support : claims 10-13

Claims 10-12 relating to a method of identifying an agent that modulates the binding of an anti-EGFR polypeptide of any of claims 1 to 9 and claim 13 relating to a kit for screening for agents that modulate EGFR - mediated disorders are speculative, not supported as required by Article 6 PCT and not disclosed in the description as required by Article 5 PCT. These claims are attempting to solve a hypothetical problem without providing a solution. As a consequence it is not considered that such claims involve inventive step.

3. Clarity

Claims 1-9 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefor are the following: the examples deal with Camelidae VHHs antibody against EGFR. The description and example convey the impression that anti EGFR polypeptide comprising at least one single domain antibody against EGFR can only be prepared as camelidae VHHs and no alternative forms are envisaged. Considering using such a terminology is possible the term "an anti-EGFR polypeptide comprising at least" is too vague and the claims are not supported by the description as required by Article 6 PCT.

Claims 8 and 9 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The following functional statements do not enable the skilled person to determine which technical features are necessary to perform the stated function: homologous sequence, a functional portion.